



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|-------------------------------|------------------|
| 10/644,588 | 08/20/2003 | Connie Sanchez | 05432/100M919-US3 | 5265 |
| 7278 | 7590 | 05/29/2009 | | |
| DARBY & DARBY P.C. P.O. BOX 770 Church Street Station New York, NY 10008-0770 | | | EXAMINER BETTON, TIMOTHY E | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1617 | |
| | | | MAIL DATE | DELIVERY MODE |
| | | | 05/29/2009 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|--------------------------------------|---------------------------------------|--|
| Office Action Summary | Application No. 10/644,588 | Applicant(s) SANCHEZ ET AL. | |
| | Examiner TIMOTHY E. BETTON | Art Unit 1617 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 March 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21, 25, 27, 31, 33, and 37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 21, 25, 27, 31, 33 and 37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' Remarks filed on 3 March 2009 has been acknowledged and duly made of record.

Claim Rejections under 35 USC § 103 are averred by applicants because said applicants' cite the following:

First, it is well established that "[e]vidence of unexpected results can be used to rebut a prima facie case of obviousness." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007). Here, escitalopram has been shown to be surprisingly superior to citalopram in the treatment of a particular patient population - namely, depressed patients having a MADRS score of at least 29, where the patients received comparable amounts of escitalopram (i.e., either the S- enantiomer alone or in its racemic form). **Evidence of these unexpected results is found in both the specification (p. 6, line 19 to p. 7, line 9) and in scientific literature that has been previously submitted in connection with this application (see, e.g., Gorman, *MedWorks Media*, 40-44 (April 2002); Lepola, *Int Clin Psychopharm*, 19:149-55 (2004); Moore, *Int Clin Psychopharm*, 20(3):131-37 (2005); Lam, *Pharmacopsychiatry*, 39:180-84 (2006); Yevtushenko, *Clinical Therapeutics*, 29(11):1-14 (2007)).** Copies of Gorman (2002), Lepola (2004), Moore (2005), and Lam (2006) were submitted with the Response filed September 27, 2007; and a copy of Yevtushenko (2007) was submitted with the Response filed August 7, 2008.

As a result, the examination of the specification upon the disclosure above is not persuasive, because it is not clear what the applicants are distinguishing based upon the pages and line numbers cited. In other words, applicants are claiming unexpected results in this current invention. However, the specification does not accurately represent what applicants' have claimed as far as unexpected results. Correlative data and cumulative results or any other representation that clearly and distinctly shows that unexpected results occurred during routine experimentation is absent and is no where represented in the specification.

Further, applicants' argue that escitalopram is substantially more than two times as potent as the racemate. However, potency does not equate to greater efficacy, it only equates to a faster onset of therapeutic activity. Now, in the case of a specific dosage of 10 milligrams of the

Art Unit: 1617

escitalopram, the specification is silent with regard to any embodiment which clearly shows unexpected results in a typical case study with the administration to a target population of an amount of 10 milligrams of escitalopram. The one of skill would reasonably conclude that racemates of a compound may produce variable side effects because of differing levels of potency. Unexpected results based on the potency in this claimed invention is not certain, because the same milligram strength of the R-enantiomer has not been adequately elucidated in the specification in such a way as to make it apparent to the one of skill that there exists a clear delineation as claimed.

Further, applicants assert that the "p" values serve as adequate and sufficient indicators that unexpected results occurred. However, the Examiner is unclear as to the correlation to surprisingly unexpected results based on arbitrary "p" values. The applicant has disclosed no specific dosage that the subjects were administered throughout the several weeks of observation.

It is not clearly established what was the specific dosage amount that was able to achieve this improved MADRS score. Further, 2.7 points of escitalopram in comparison to 1.5 points for citalopram (page 7 of spec.) is notable, but the specific detail which clearly indicates unexpected results is absent. It is uncertain as to what is the specific amount of escitalopram in milligrams required in order to achieve the significant change in the MADRS score in a patient in comparison to the same, greater, and/or lesser amount of citalopram.

The clinical study of page 6 is deficient in showing any indication of superior results of escitalopram as opposed to citalopram.

Routine experimentation would be expected to achieve the claimed limitation of the current invention directed to alleged unexpected results.

Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21, 25, 27, 31, 33, and 37 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Patris M, et al. ("Citalopram versus fluoxetine; a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice," 1996 International Clin Psychopharm 11: 129-136), in view of Boegesoe et al. (US Pat. 4,943,590), and further in view of Maisy et al. (US Pat. 4,079,135).

Patris et al. teach the administration of citalopram in the treatment of patients with major depression (abstract). Patients had a score of 30 on the MADRS at the beginning of the 8-week treatment period (see Fig. 1 p. 132). The reference teaches assessment of the efficacy of treatment by measuring the MADRS score as well as by the CGI severity and improvement scale (see pp. 130 and 134).

Patris et al. do not teach escitalopram (the S-enantiomer) specifically.

Boegesoe et al. teach that antidepressant drug citalopram has two enantiomers, (+)-citalopram (which is escitalopram) and (-)-citalopram, and that the entire 5-HT uptake inhibition activity resides in the (+) enantiomer (i.e. escitalopram) (see: abstract; col. 1, lines 1-28; col. 2, lines 9+). The reference also teaches separation of the two enantiomers to yield pure citalopram enantiomers (see col. 2, lines 51 - col. 7, line 25). The reference teaches, "a method for alleviating depression in a living animal body subject thereto" by administering an effective amount of the compound or pharmaceutically acceptable salts (which is escitalopram), at dosages ranging from 0.10-100 mg and preferably 5-50 mg daily (overlapping the dosage of current claim 25). (See: abstract; col. 8 Table 1; col. 8, lines 55-66; claims 1-2 & 7-12).

While Boegesoe et al. teach pharmaceutically acceptable salts; the reference does not teach oxalate salts specifically.

The deficiency of Boegesoe is resolved by the teachings of Maisey.

Maisey teaches a method of relieving or preventing depression in warm-blooded animals, including man, which comprises administering thereto an anti-depressant effective amount of a compound of the formula: ##STR36## wherein R.sup.1 is hydrogen or halogen, or alkyl or alkoxy of 1 to 3 carbons; A is a radical of the formula: ##STR37## wherein R.sup.2 and R.sup.3, which may be the same or different, are hydrogen or alkyl of 1 to 3 carbons and B is oxygen; and the non-toxic, pharmaceutically-acceptable acid-addition salts thereof in association with a major amount of a non-toxic, pharmaceutically-acceptable diluent or carrier (col. 16, l. 42)

Maisey teaches an embodiment which suggests and supports that conversion to a crystalline oxalate salt is a standard **procedure** (col. 9, l/s 56 and 57)

Maisey does not teach escitalopram but it does teach an agent indicated for treating depression.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to use the oxalate or crystalline oxalates salt of escitalopram in the instantly claimed method of treating severe depression, having been taught by the prior art that it is known to make oxalate and crystalline oxalate salts of a racemic compound to obtain the (S) isoform and motivated by the desired to obtain the (S)/(+) isoform salt of citalopram (i.e. escitalopram), which is known to be the racemate wherein the pharmaceutical antidepressant activity resides. Patris establishes the fact that within citalopram is contained the (S)-enantiomer which is escitalopram. Boegesoe definitively teaches the subject matter of the claimed invention, because Boegesoe addresses and encompasses the bioactive agent and dosage parameters of the claimed invention. Further, based on the teachings of Maisey the conversion of a compound indicated for depression to a more pure compound is disclosed as a standard procedure. As mentioned before, the limitations of the instant claims drawn to a salt species are functional language and hold no patentable weight in view of claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

Art Unit: 1617

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY E. BETTON whose telephone number is (571)272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Application/Control Number: 10/644,588
Art Unit: 1617

Page 8

TEB

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617